Enrolling Decisionally Incapacitated Subjects in Neuropsychiatric Research

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ABSTRACT

This paper discusses the National Bioethics Advisory Commission's (NBAC's) report on research involving persons with mental disorders that may affect decisionmaking capacity. After placing the NBAC recommendations into their historic context, the authors propose a strategy to enroll decisionally incapacitated subjects into neuropsychiatric research. The authors maintained that their proposed consensus model for research authorization, utilizing subject advocates, fosters valuable clinical research while protecting potentially vulnerable subjects.

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INTRODUCTION

There is perhaps no thornier issue in research ethics than finding the right balance between protecting human subjects and ensuring access to clinical research. This is especially difficult in subject populations with neurological or psychiatric disorders that impair an individual's ability to engage in the process of informed consent.

In this paper, we will address the question of research with this population and examine critically the National Bioethics Advisory Commission's (NBAC's) 1998 report[1] on research involving persons with mental disorders that may affect decisionmaking capacity. Our aim is to build upon the NBAC recommendations and suggest a more contextually responsive approach to the regulation of neuropsychiatric research that both protects this vulnerable population and fosters valuable clinical research.[2] To this end, we propose a consensus model of authorization for involving decisionally incapacitated subjects.

REGULATING CLINICAL RESEARCH: AN HISTORICAL PERSPECTIVE

To place the NBAC's report in context, it is helpful to compare NBAC's work in this area with the approach of its predecessor, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, created by Congress under the National Research Act of 1974. Their efforts were largely a response to well-publicized revelations about the Tuskeegee Syphilis Study and research ethics abuses documented by Henry Beecher.[3]

The National Commission's Belmont Report[4] articulated three ethical principles that should govern biomedical research. It stressed the centrality of respect for persons, beneficence, and justice and the associated applications of these principles in the process of informed consent, risk/benefit assessment, and selection of subjects. Respect for persons was especially important for vulnerable or captive populations whose ability to provide consent might be compromised. To this end the National Commission emphasized special protections that would safeguard the decisionally incapacitated, mentally ill, institutionalized persons, minors, prisoners, and also pregnant women, who could be exploited by the research community.

The National Commission, given its historic context, sensibly focused on protecting potential research subjects. The goal was not to promote access to clinical research but to ensure that research adhere to the constraints of ethical principles and regulatory safeguards, most notably prior and continuing review of research by Institutional Review Boards (IRBs). The Belmont Report asserted that vulnerable populations could no longer be used as convenient fodder for research studies simply because they were available in institutional settings. Invoking the principle of justice, Belmont stated that the burden of research should be fairly distributed. If vulnerable subjects were to be enrolled in research, investigators and IRBs would need to provide adequate justification for their involvement to ensure that they were not exploited.

In the 20 years since the National Commission operated, its principled approach to research ethics has led to enhanced regulations and ethical guidance that has helped to prevent research abuses, increase subject safety, and establish institutional mechanisms to stem transgressions from ethical norms articulated in its reports. Despite this progress, revelations of earlier research abuses motivated the creation of a new national bioethics commission to examine and make policy recommendations concerning human subjects research. In the early 1990s the news media broke another story of research abuses involving government-sponsored studies exposing human subjects to

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radiation without their knowledge or consent from World War II through the Cold War.[5] These revelations led President Clinton to establish an Advisory Committee on Human Radiation Experiments (ACHRE).[5] ACHRE's work led the President to establish a more permanent National Bioethics Advisory Commission (NBAC).

NBAC: PAST AS PROLOGUE

It is important to observe that the while the NBAC was established in 1995, its work was stimulated by revelations about decades-old research abuses that were contemporaneous with those that led to the establishment of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in the 1970s. Furthermore, the NBAC has sought to follow up on the National Commission's earlier recommendations on research involving "the institutionalized mentally infirm" which were never incorporated into federal regulations.[6]

This shared history has led the NBAC to emulate the National Commission in salient ways. Like the National Commission, the NBAC has been extremely sensitive to the historic legacy of research abuses and believes that these deviations from ethical norms can best be addressed through a strong regulatory stance.

This orientation is apparent in the NBAC's decision to author a report on research in subjects with impaired decisionmaking capacity. It justified its focus on that subset of such subjects who are mentally ill by stating that it "...has chosen to focus this report on persons with mental disorders, in part because of this population's difficult history of involvement with medical research. Moreover, NBAC believes that in addition to the regulations that are already applicable, research involving subjects with mental disorders that may affect decisionmaking capacity should be governed by specific further regulations."[7]

The presumption in this statement, and in the tenor of NBAC as a whole, appears to be that contemporary ethical challenges in neuropsychiatric research are best understood through historical analogy and that a protectionist approach to research regulation is best suited to govern this complex enterprise. We maintain that while the historic abuse of individuals with impaired decisionmaking should inform our understanding of ethical norms and proper research conduct, a protectionist regulatory stance does not provide fully adequate ethical guidance for the present research context. It is just as critical to have a clear understanding of the relevant scientific and clinical contexts in order to make informed judgments about the risks and benefits of proposed clinical research with vulnerable groups of subjects. Such a protectionist approach can lead to unworkable regulatory schemes that have the potential to severely curtail important research in the neurosciences that may directly benefit individuals with neurological and psychiatric disorders or lead to their improved treatment in the future.

To promote protection of research subjects at the cost of access to valuable research may deprive incapacitated individuals of interventions that have the potential benefit of promoting independence and self-determination by restoring or augmenting cognitive function. The proposed use of deep brain stimulation and other neuromodulation techniques are promising examples of such work.[8-10] We suggest that the ethical principles of respect for persons, beneficence, and justice may be understood as encouraging, clinically promising, and carefully designed research with decisionally incapacitated subjects as well as protecting them from abuse.

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NBAC RECOMMENDATIONS

The NBAC report endeavors to close a perceived gap in human subjects protections: the lack of explicit guidelines for research involving persons at risk of losing decisionmaking capacity. Although NBAC's report has been recognized as making a valuable contribution to public debate on this complex topic, its recommendations have been criticized for unduly impeding needed research in neurology and psychiatry.[11,12]

We focus our ethical analysis on the scope of NBAC's recommendations, the risk/benefit categories that are connected with its regulatory safeguards, and its guidelines for authorizing the enrollment of decisionally incapacitated subjects in research. We do not address here the important issues of procedures for assessing capacity to give informed consent[13] or ethical problems associated with particular study designs.[14,15]

NBAC's recommendations are explicitly concerned with research on mental disorders. For studies involving persons with mental disorders that may affect

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decisionmaking capacity, NBAC recommended three regulatory categories: (1) research presenting minimal risk; (2) research presenting greater than minimal risk that offers the prospect of direct medical benefit to subjects; and (3) research presenting greater than minimal risk without offering the prospect of direct medical benefit. Within each of these categories, NBAC relies upon "legally authorized representatives" to provide permission for enrolling decisionally incapacitated subjects in justifiable research studies. Legally authorized representatives are defined as "an individual authorized by law (statutory or judicial) or previously published institutional rules to make medical decisions on behalf of another person."[16]

For research involving minimal risk, a legally authorized representative could consent to enrollment in research of a decisionally incapacitated subject with or without the subject's "prospective authorization" for research. Prospective authorization is understood here as an individual's specified advance directive indicating preferences for research participation in case of loss of decisionmaking capacity. For protocols presenting greater than minimal risk that offer the prospect of direct medical benefit to the subjects, the legally authorized representative would also be able to give permission for enrollment in research with or without prospective authorization. However, in protocols that involved greater than minimal risk without the prospect of direct medical benefit, the legally authorized representative could only give permission for study enrollment when the subject had also given prospective authorization for the research. Research in this risk/benefit category, with permission of the legally authorized representative but without prospective authorization, could only be approved by a Special Standing Panel (SSP) convened by the Secretary of Health and Human Services or by the local IRB pursuant to as yet unwritten SSP guidelines regarding approvable research.

NBAC's recommendations are problematic for several reasons. First, by defining the scope of its report in terms of "mental disorders," the guidelines do not explicitly address research with other groups of human subjects potentially at risk for loss of decisionmaking capacity, including those with brain tumors, traumatic brain injury, mentally incapacitating neurological disorders, and patients taking medications that produce cognitive impairment. This narrow scope is not only arbitrary, it risks stigmatizing patients with mental disorders by requiring more stringent protections for research with this group of human subjects as compared with other groups who are just as vulnerable.

Second, reliance on the dichotomy of minimal risk and more than minimal risk does not provide a sufficiently graded set of risk categories to encompass the spectrum of clinical research.[2,12] In consequence, it groups together study designs that pose only slightly more than minimal risk, such as positron emission tomography scans using low doses of radiation and higher risk research, such as "challenge" studies that provoke distressing symptoms. Some commentators have recommended inclusion of a third research risk category—studies posing a minor increment over minimal risk.[2,12] This is a feature of the federal regulations governing research involving children.[17]

A third problem is the NBAC's reliance on the regulatory distinction between research that does and does not offer the prospect of direct medical benefit, which has a significant bearing on the safeguards required for permitted research. Whereas phase III clinical trials, which seek to test the efficacy of experimental treatments, will readily be understood as having the prospect of direct medical benefit, the categorization of other types of clinical research is less clear. In fact, the line between beneficial and nonbeneficial research is often blurred, especially at the frontiers of clinical investigation. Phase I clinical trials offer the prospect of direct medical benefit in the sense that there is a chance, though small, that some subjects will receive clinically significant improvement. The purpose of this stage of research, however, is to test the safety of treatments by determining the maximum tolerated dose of experimental medications. Nonetheless, investigators may see phase I studies as having a "therapeutic intent."[18]

How, then, should phase I studies be classified with respect to the prospect of benefit? Other studies that offer no prospect of direct benefit may be linked with clinical interventions that do offer therapeutic benefit.[19] Viewing research as either directly beneficial or not directly beneficial once again adopts a rigid and somewhat artificial dichotomy to characterize research that falls along a continuum. Moreover, because research classified as

having a prospect of benefit requires less stringent regulatory safeguards in the NBAC framework, reliance on this dichotomy may reinforce the already pervasive tendency to overemphasize the potential for therapeutic benefit from research participation.[20,21]

Fourth, prospective authorization is plausible in only some medical conditions. Prospective authorization is possible in some neuropsychiatric illnesses, such as incipient dementia when preferences about research participation can still be ascertained or in psychotic disorders, which have periods of symptomatic fluctuation when decisionmaking capacity may be present and when potential subjects may be asked about their willingness to participate in research. It has limited utility, however, when loss of capacity is unanticipated or a symptom of a long-standing disorder. When loss of capacity follows an acute head trauma or stroke or is a preexisting condition, such as advanced Alzheimer's disease, potential subjects will not have had the opportunity to prospectively authorize their future involvement in research studies.

Indeed, even if individuals could anticipate cognitive impairment, few Americans are likely to engage in such research advance care planning. At present it is estimated that less than 20% of adults have an advance directive to direct *routine* health care in the event of decisional incapacity.[22] Given the public's unfamiliarity with clinical research and its penchant for the denial of disability, it is unlikely that many adults will engage in prospective authorization for clinical research in the event of decisional incapacity.[23] Furthermore, empirical studies suggest that health care proxies are poorly informed about the research preferences of their charges and that any decisions about enrollment would be more reflective of the proxy's decision about their own participation.[24]

In summary, the NBAC recommendations do not offer an adequate ethical framework for responsible neuropsychiatric research. The scope of the recommendations is too narrow, the risk categories are truncated, the sharp distinction between beneficial and nonbeneficial research seems elusive, and the reliance on prospective authorization has limited practical utility. The NBAC's regulatory categories are not well suited to accommodate the contextual reality of neuropsychiatric disorders and neuropsychiatric research.

A CONSENSUS MODEL FOR SURROGATE RESEARCH AUTHORIZATION

Decisionmaking regarding research with subjects incapable of informed consent operates at two levels. At a macro level, IRBs must determine the justifiability of including a group of decisionally incapacitated subjects in specific research studies in view of the scientific questions to be answered, the risks, and the prospect of direct medical benefits to the subjects. At a micro level, ethically appropriate decisions need to be made to enroll *specific* individuals incapable of giving informed consent in IRB-approved studies. We focus here on the latter, whether an individual subject who is decisionally incapacitated should be enrolled in a research study.

In response to the limitations of NBAC's recommendations, we offer a procedural model for surrogate research authorization for the decisionally incapacitated that seeks to protect subjects adequately and at the same time allows valuable research to go forward. As an alternative to NBAC's complex regulatory scheme that depends upon prospective authorization and an untested national SSP, we propose a collaborative model of decisionmaking that seeks to reach a reliable consensus on decisions about subject enrollment in clinical research.

In our framework, decisions about enrollment of a decisionally incapacitated subject in an IRB-sanctioned clinical protocol that presents more than minimal risk would require the agreement of the subject's legally authorized representative and physician, the clinical investigator, as well as a lay volunteer *subject advocate* who has had experience as a surrogate decision maker for an intimate with a similar disorder. For enrollment of incompetent subjects in minimal risk research, the permission of the subject's legally authorized representative would suffice, provided that the subject does not dissent. The recommended consensus model would apply to research that is more than minimal risk with or without a prospect of direct medical benefit.

The use of subject advocates to assist in clinical decisionmaking for decisionally incapacitated individuals has a precedent in the efforts of the New York State Commission on Quality Care for the Mentally Ill.[25] This commission, established by the New York State Legislature, oversees the use of volunteer Surrogate Decision-Making Committees

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(SDMCs) that are empowered to make major medical decisions for incompetent mentally disabled persons who have neither family member nor guardian to provide consent for treatments.

As established by statute, these SDMCs are composed of 12 members and operate in units of four individuals. Each unit must have a diverse membership with representation from each of the following categories: physicians, nurses, certified social workers, or other NY State licensed health care professional; former patients or the close adult relatives of mentally disabled persons; practicing attorneys; and advocates for the mentally disabled and others with recognized expertise or demonstrated interest in the care and treatment of mentally disabled persons.[26] The use of these SDMCs is intended as an alternative to the judicial process and "...is intended to provide a quicker, more easily accessible, inexpensive and more personalized decision on behalf of mentally disabled individuals."[27] Data from this alternative decisionmaking process have been encouraging.[28]

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The model that we are suggesting is different from SDMCs in use in New York State in that our proposal would consider decisions involving research and not therapy and that our recommendations are meant to assist legally authorized representatives with the weighty task of deciding whether subject enrollment is appropriate. Nonetheless, the experience of the SDMCs is instructive because it addresses vulnerable decisionally incapacitated individuals, relies upon lay advocates, and promotes a collaborative and consensus generating process.[29]

Placing the nexus of decisionmaking for a decisionally incapacitated subject into this collaborative framework draws upon the skills, expertise, and experience of each of these interlocutors while attempting to counterbalance the biases and motivations of each. To appreciate how this constellation of individuals might best assess the interests of a decisionally incapacitated individual under consideration for enrollment in a clinical trial, it is necessary to delineate the strengths and weaknesses of each of its members.

The legally authorized representative brings personal knowledge of the potential subject and may have knowledge of his/her preferences regarding health care and possibly clinical research. The legally authorized representative will also know something of the subject's personal, cultural, and religious beliefs—all important attitudes and values that might inform a "substituted judgement" of what the subject might have decided about enrollment into a research study. On the other hand, the subject's legally authorized representative may be the patient's primary caregiver and carry the burden of caregiving.[30] It is well appreciated that surrogates of individuals who have sustained serious head injury go through phases of anger, acceptance and denial about the condition of their loved ones.[31-33] Comparable factors may influence the perceptions of family members of individuals with dementia or schizophrenia. These factors may create unappreciated conflicts of interest that could distort decisionmaking about enrollment in a research study and result in secondary gain.

The patient's physician, as distinguished from the physician-investigator, brings knowledge of the subject's medical condition to the deliberative process. This knowledge begins with an assessment of the nature, duration, and severity of decisional incapacity and may also encompass knowledge of the patient before cognitive impairment precluded the subject's involvement in informed consent. The patient's physician also conceivably brings an element of technical knowledge relevant to understanding the proposed research study without any personal investment in the research, in contrast to the physician-investigator. The use of the subject's physician is consistent with the NBAC's recommendation that the legally authorized representatives have access to an independent health care professional to advise them about enrollment in a study protocol with more than minimal.[34] The value of the patient's physician's perspective could be limited by any preexisting relationship between the physician and the research team, which could create a conflict of interest.

The clinical investigator is an essential member of this decisionmaking colloquium. As principal investigator for the research, she is ultimately responsible for the conduct of the investigation. She is knowledgeable about the study protocol and best positioned to know whether or not a potential subject meets study inclusion or exclusion criteria. She can answer questions about the protocol, its potential risks and benefits, as well as alternatives. These qualifications are mitigated, however, by the inherent conflict of interest that attends

the role of the clinical investigator, who is committed to scientific work and thus has a vested interest to promote study enrollment. Given this bias, complete objectivity may not be possible.

The subject advocate is perhaps the most novel member of this decisionmaking colloquium.[35] For this role, we envision someone who is knowledgeable about the subject's illness or disability and who has had experience making decisions as a surrogate for a family member or close friend with this disorder. These volunteers could draw upon their experiences as surrogates and have a perspective that is both sympathetic to the burdens of the legally authorized representative yet detached from those responsibilities. The unique experience of these volunteers could make them more or less receptive to clinical research. The inclusion of a subject advocate in this deliberative process parallels NBAC's recommendation that IRBs that regularly review protocols for research involving persons with mental disorders should include at least one member who is from "the population being studied, a family member of such a person, or a representative of an advocacy organizations for this population."[36]

These subject advocates could be drawn from a pool of volunteers associated with an institution where the subject is receiving care. Social work staff could help to match these volunteers with legally authorized representatives so that each felt comfortable with the other. The subject advocate's role would be to help the legally authorized representative with difficult choices and to serve as a counselor or mentor with whom the legally authorized representative would find trustworthy and supportive. In addition, they would be advocates for the proposed subject charged with seeking evidence of relevant prior preferences of the subject about research participation and helping to interpret these preferences if they were available.

From this discussion of the strengths and weaknesses of each of these decision makers, it becomes apparent that while each can make a valuable contribution, no single individual has the knowledge, skills, or perspective necessary to make a unilateral judgment about the ethical propriety of study enrollment. Collectively they can come together to reach a carefully considered decision.

For these reasons, this process would seek to achieve a consensus of all involved in the colloquium. While study enrollment could not proceed without the expressed permission of the legally authorized representative, the legally authorized representative's prerogative to provide permission would not stand alone. It would require the concomitant agreement of the subject's physician, the clinical-investigator, and the subject advocate. In this way the legally authorized representative (and all involved) would be urged to view this deliberative process as one that should seek to reach a consensus on study enrollment, weighing the potential risks and benefits along with evidence of the incapacitated subject's values and preferences.

This proposal should not be understood as an adversarial one undermining the authority of the legally authorized representative but rather as a process that is offered to serve as a sanctioned aid for decisionmaking that supports the legally authorized representative while protecting the interests of the potential subject.

CONCLUSION

We suggest that, along with IRB review and approval of research studies, the proposed consensus mechanism provides an ethically adequate framework for enrolling decisionally incapacitated individuals in valuable clinical research. CNS

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